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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,114	02/25/2004	Masaaki Goto	16991.016	2626

28381 7590 07/27/2006

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/785,114	GOTO ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *32-37* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/915,004.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *14 October 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 25 February 2004 in the disclosure and claims have been entered in full. Claims 1-31 have been canceled. New claims 32-37 have been added.

The amendment of 3 May 2006 has been entered in full. Claims 32-37 have been amended.

Election with traverse

2. Applicant's election with traverse of Group I, claims 32, 34-35 and 37, in the reply filed on May 3, 2006 is acknowledged.

3. The traversal is on the ground(s) that all the method claims 32-37, which include the non-elected Group II, encompassing claims 33 and 36, could be searched and examined as a "single entity" without undue burden. Applicants note that the pending claims were "searched and examined together in the parent application (US Application No. 10/232,858, now U.S. Patent No. 6,855,808)". This is found persuasive in part because claims 33 and 36 are broadly interpreted by examiner to read upon gene therapy and protein therapy. Claims 33 and 36 are rejoined in part and will be examined to the extent that they read upon administration of an OCIF protein. Furthermore, each patent application is examined on its own merits. The invention that was deemed allowable in one patent has no bearing on this application.

This requirement is still deemed proper and is therefore made FINAL.

4. Applicant timely traversed the restriction (election) requirement in the reply filed on May 3, 2006.

5. Claims 32-37 drawn to a method comprising administration of a polypeptide or a pharmaceutical preparation comprising OCIF protein are being considered for examination in the instant application.

IDS

6. The IDS submitted on 14 October 2004 has been considered by Examiner. However, the International Search Report citations (AJ and AK – page 10) could not be located in the parent application and have been crossed off in the IDS.

Specification

7. The disclosure is objected to because of the following informalities:

A) An updated status of the parent patent application should be included in the first sentence of the specification. A statement reading, "This application is a continuation of U.S. Serial No. 10/232,858, filed September 3, 2002, "now U.S. Patent No. 6,855,808" should be entered. Appropriate correction is required.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing bone mass comprising administering a pharmaceutical preparation comprising the OCIF protein of SEQ ID NO: 5 to increase bone mass, does not reasonably provide enablement for improving decreased bone mass by administering 'an' OCIF protein encompassing its variants or fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. The claims are directed to a method improving decreased bone mass or density by administering in humans: a) a pharmaceutical preparation containing 'an' OCIF protein encoded by SEQ ID NO: 6, or 'an' OCIF protein (claims 32, 35); b) a pharmaceutical preparation for 'an' introducing 'an' OCIF protein encoded by SEQ ID NO: 6, or 'an' OCIF protein (claims 33, 36); c) 'an' OCIF protein encoded by SEQ ID NO: 6, or 'an' OCIF protein (claims 34, 37). It is noted that the Examiner has broadly interpreted the phrases "an OCIF protein encoded by SEQ ID NO: 6" (claims 32-34) and "an OCIF protein" (claims 35-37) to encompass any OCIF protein, variant, or fragment.

10. The specification of the instant application teaches an OCIF protein comprising 401 amino acid residues of SEQ ID NO: 5 (Sequence Listing, page 4), encoded by SEQ ID NO: 6 that plays a role in bone resorption (page 3, para 10; pages 27-32, para 119-132; Example 16). The specification also demonstrates the biological activity of OCIF using 293/EBNA cells (human embryonic kidney cells), stromal and mouse spleen cells by measuring acid phosphatase positive cells (page 22, para 96,97; page 29 para 124). The specification further discloses that OCIF enhances mechanical strength of bones in six-week old male rats after denervation of the forelimb (page 10, para 44; page 63, para 256-260; Example 26; Figure 15). The specification further suggests the use of OCIF protein in pharmaceutical preparations for improving decreased bone mass in diseases, for example osteoporosis (page 10, para 45). Additionally, the specification teaches the cloning of OCIF variants such as OCIF2, OCIF3, OCIF4 and OCIF5 (page 8, para 35; pages 34-37, para 141-166; Figures 9-12). However, the specification does not teach any methods or working examples to indicate that all possible OCIF fragments and variants elicit improvement in disorders related to decreased bone mass or density. Undue experimentation would be required of the skilled artisan to determine such. The specification does not teach the specific polypeptide domains necessary for preserving OCIF biological activity, in this case reducing bone resorption. Furthermore, the specification does not teach functional or structural characteristics of the fragments and variants of OCIF recited in the claims other than the polypeptide comprising the full-length and "mature" amino acid

sequence of SEQ ID NO: 5. It is not clear from the relevant pre and post-filing date literature as to what regions of the OCIF sequences or the maximum length of the sequences are essential for biological activity. Thus, undue experimentation would be required of the skilled artisan to identify the precise structural characteristics of OCIF fragments and variants showing inhibition of bone resorption activity.

11. Additionally, regarding claims 35-37, the instant fact pattern is similar to that in *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), wherein a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). The specification discloses four variants of OCIF (OCIF2, OCIF3, OCIF4, OCIF5) polynucleotides (SEQ ID NOs: 8, 10, 12 and 14) and polypeptides (SEQ ID NOs: 9, 11, 13 and 15). The specification also discloses OCIF mutant polypeptides (SEQ ID NOs: 62-82) (page 53, para 219). However, the claims fails to recite any sequence limitations, and thus the skilled artisan would have to resort to trial and error experimentation to identify proteins meeting the functional limitations of the claims.

12. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the OCIF proteins which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be

predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

13. Due to the large quantity of experimentation necessary to generate the infinite number of OCIF fragments and variants recited in the claims and screen the same for improvement of decreased bone mass activity; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations - undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

14. Claims 32-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

15. Claims 32-37 are directed to a method improving decreased bone mass or density by administering in humans: a) a pharmaceutical preparation containing 'an' OCIF protein encoded by SEQ ID NO: 6, or 'an' OCIF protein (claims 32, 35); b) a pharmaceutical preparation for 'an' introducing 'an' OCIF protein encoded by SEQ ID NO: 6, or 'an' OCIF protein (claims 33, 36); c) 'an' OCIF protein encoded by SEQ ID NO: 6, or 'an' OCIF protein (claims 34, 37). It is noted that the Examiner has broadly interpreted the phrases "an OCIF protein encoded by SEQ ID NO: 6" (claims 32-34) and "an OCIF protein" (claims 35-37) to encompass any OCIF protein, variant, or fragment. The claims require that the OCIF protein sequences generated as stated above possess the activity to improve decreased bone mass, however, the claims do not require that the polypeptide sequences possess any particular conserved structure, or other disclosed distinguishing feature.

16. The specification of the instant application teaches an OCIF protein consisting of 401 amino acid residues of SEQ ID NO: 5 (Sequence Listing, page 4), encoded by SEQ ID NO: 6 which has a role in bone resorption (page 3, para 10; pages 27-32, para 119-132; Example 16). The specification also discloses the in vivo effect of OCIF on increasing the mechanical strength of bones in rats after denervation of the forelimb (page 10, para 44; page 63, para 256-260; Example 26; Figure 15). The specification also suggests the use of OCIF protein in pharmaceutical preparations for improving decreased bone mass in diseases,

for example osteoporosis (page 10, para45). In addition, the specification teaches the cloning of OCIF variants such as OCIF2, OCIF3, OCIF4 and OCIF5 (page 8, para 35; pages 34-37, para 141-166; Figures 9-12).

17. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The specification has not shown a relationship between the structure, function, or properties of the claimed genus of polypeptides. However, in this case, the only factor present in the claim is a recitation of functional activity. There is not even identification of any particular portion of the OCIF structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The brief description in the specification of one OCIF polypeptide (SEQ ID NO: 5) is not adequate written description of an entire genus of functionally equivalent polypeptides, which incorporate all fragments, and variants of OCIF.

18. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the

art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

19. With the exception of the OCIF sequences referred to above (SEQ ID NO: 5), the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The *polypeptide itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

20. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

21. Therefore, only the OCIF polypeptide comprising the amino acid sequence of SEQ ID NO: 5, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112-Second paragraph

22. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claims 32, 33, 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

24. The terms "improving" and "improvement" in claims 32, 33, 35 and 36, is a relative term, which renders the claim indefinite. The terms "improving" and "improvement" are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. First, the term "decreased bone mass" requires a point of reference and none is given. By comparison, the limitation "increased bone density" in claim 34 and 37 is not vague because one would understand that it requires an increase in bone density relative to the density of a subject's bone prior to the administration the protein referred to therein. No such point of reference is understood for the limitation "decreased bone mass" as it is employed in claims 32, 33, 35 and 36. Second, the term "improving" is vague because it requires a reference of an objective. For example, if one wished to decrease the bone mass in an individual, an acceleration in a rate of bone loss would be an improvement. However, if one wished to prevent or inhibit bone loss, then a reduction or reversal in a rate of bone loss would be an improvement.

Double Patenting

25. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

26. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

27. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

28. Claims 32-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32, 33, 35 and 36 of copending Application No. 10/979,654. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to administration of an OCIF polypeptide. The claims of the 10/979,654 application recite the treatment of bone diseases (osteoporosis, rheumatism) and abnormal bone metabolism while the claims in the instant case recite improving decreased bone mass and increasing levels of an OCIF protein. The claims of the '654 application recite the administration of any OCIF protein while claims 35-37 of the instant application similarly recite the administration of any OCIF protein. Claims 32-34 of the instant application recite the administration of an OCIF protein encoded by SEQ ID NO: 6.

29. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

30. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Tobias et al. Expert Opin. Ther. Targets. 6: 41-56, 2002.
(Reference showing the advantages and disadvantages of OPG use as a therapeutic agent for osteoporosis).

Bekker et al. J Bone Mineral Res 16, 348-360, 2001.
(Reference showing the inhibition of bone resorption by a single dose of genetically engineered OPG-Fc construct (Fc fragment of immunoglobulin) in post-menopausal women).

Simonet et al, Cell 89: 309-319, 1997
(Reference showing expression of OCIF in different tissues such as heart, lung, kidney liver and placenta of humans and animals).

Takahashi et al. Biochem Biophys Res Comm 256, 449-455, 1999
(Reference showing the overexpression of OPG or injection of OPG/OCIF increased bone mass and decreased bone resorption).

Egermann et al. Osteoporosis Int, 16: S129-S138, 2005
(Reference showing the animal models for studying bone mineral density and mechanical strength in osteoporosis).

Hofbauer et al. JAMA, 292: 490-495, 2004

(Reference showing that bone loss can result from numerous pathologies involving different regulatory mechanisms of OPG)

Hofbauer et al. J of Clin Endocr Metab, 85: 2355-2363, 2000
(Reference showing that in vivo modulation of OPG could result in extreme phenotypes, such as osteoporosis and osteopetrosis)

Hamdy. Current Rheumatol Rep, 8: 50-54, 2006
(Reference showing the state of clinical trials for OPG in bone diseases like osteoporosis)

Yano et al. J of Bone Mineral Research 14, page 518-527, 1999
(Reference showing the age-related increase of OPG/OCIF in serum of men and women)

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

33. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
July 14, 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER